

BMJ Open Psychological and support interventions to reduce levels of stress, anxiety or depression on women's subsequent pregnancy with a history of miscarriage: an empty systematic review

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ABSTRACT

Objective The aim of this systematic review was to assess the effect of interventions to reduce stress in pregnant women with a history of miscarriage.

Design A systematic review of randomised controlled trials (RCTs).

Data source A total of 13 medical, psychological and social electronic databases were searched from January 1995 to April 2016 including PUBMED, CENTRAL, Web of Science and EMBASE.

Eligibility criteria This review focused on women in their subsequent pregnancy following miscarriage. All published RCTs which assessed the effect of non-medical interventions such as counselling or support interventions on psychological and mental health outcomes such as stress, anxiety or depression when compared with a control group were included. Stress, anxiety or depression had to be measured at least preintervention and postintervention.

Results This systematic review found no RCT which met our initial inclusion criteria. Of the 4140 titles screened, 17 RCTs were identified. All of them were excluded. One RCT, which implemented a caring-based intervention, included pregnant women in their subsequent pregnancy; however, miscarriage was analysed as a composite variable among other pregnancy losses such as stillbirth and neonatal death. Levels of perceived stress were measured by four RCTs. Different types of non-medical interventions, time of follow-up and small sample sizes were found.

Conclusion Cohort studies and RCTs in non-pregnant women suggest that support and psychological interventions may improve pregnant women's psychological well-being after miscarriage. This improvement may reduce adverse pregnancy-related outcomes in subsequent pregnancies. However, this review found no RCTs which met our criteria. There is a need for targeted RCTs that can provide reliable and conclusive results to determine effective interventions for this vulnerable group.

INTRODUCTION

Recent studies have focused on the effect of women's psychological well-being during pregnancy and its effects on the mother and

Strengths and limitations of this study

- To our knowledge, this is the first attempt to systematically look at the psychological effect of non-pharmacological interventions on pregnant women with a history of miscarriage.
- This systematic review increases the awareness of the 'evidence gap' in this vulnerable group.
- It also highlights the clinical importance of including pregnant women in randomised controlled trials and proposes reasons why different types of pregnancy loss should be investigated separately.
- However, this review was limited by the unexpected result and no further analysis could be completed.

infant.^{1–3} Women are highly reactive to stress in early pregnancy.⁴ Approximately 25% of women report emotional distress during the antenatal period.⁵ Given the importance of maternal psychological well-being for predicting outcomes, it is necessary to effectively examine appropriate interventions to reduce stress in pregnancy.⁶ Very recently, the UK National Institute for Clinical Excellence called for randomised controlled trials (RCTs) to evaluate interventions aimed at tackling moderate to severe psychological disorders in the pregnant population.⁶

Studies on stress during pregnancy have established that psychological stress might be associated with an increased risk of a number of adverse pregnancy outcomes, such as preterm labour and low birth weight.^{1 7–9} Change in pregnancy-specific stress between the second and third trimester has been significantly associated with an increased likelihood of preterm deliveries^{9–11} and with implications for fetal development.^{12 13} These outcomes are among the leading causes of infant mortality and health problems which

may persist not just into childhood but throughout their adult lives.⁷

Miscarriage is one of the most common complications during early pregnancy.^{14 15} It is estimated that miscarriage occurs in 20% of all clinically recognised pregnancies^{16 17} and up to half of all pregnancies.¹⁸ Experience of miscarriage may alter women's psychological and mental health and well-being.^{6 19} Miscarriage has been associated with increased levels of distress,^{20 21} anxiety and depression.^{22–29} In some cases, the psychological symptoms of anxiety and depression can persist for up to 1 year after miscarriage.^{26 30–33} In addition, it is increasingly recognised that the adverse psychological and mental health consequences of previous miscarriage continue after the loss and into subsequent pregnancies.^{22 34 35} Some examples of the evidence found in the literature included higher levels of psychological distress,^{36–40} pregnancy-specific anxiety^{38 41–44} and depressive symptoms.^{44 45}

However, few studies have evaluated the beneficial effect of psychological and supportive care in pregnant women who have had miscarriage and who are in their subsequent pregnancy. In a cohort study, Clifford *et al* (1997) found that pregnant women who followed a specific antenatal counselling support plan had a significantly higher pregnancy success rate than those who did not participate.⁴⁶ Similar results were found in two other cohort studies carried out with women who experienced recurrent miscarriage,^{47 48} which is defined as three or more consecutive pregnancy losses.⁴⁹ These studies indicate the potential importance of providing support for women in a subsequent pregnancy following miscarriage.^{21 50} Therefore, the aim of this systematic review was to examine the literature to explore the effect of psychological and support interventions to reduce levels of stress among pregnant women who have a history of miscarriage.

METHODS

The Cochrane Handbook for Systematic Reviews of Interventions,⁵¹ the Cochrane Consumers and Communication Review group for data synthesis and analysis⁵² and The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline⁵³ were adhered to for conducting and reporting this systematic review (see online supplementary file 1). This systematic review has not been registered in the international prospective register of systematic reviews (PROSPERO) database.

Eligibility criteria

Criteria for considering studies for this systematic review were:

Type of studies

All published RCTs, including cluster RCT, were systematically searched in this review. Controlled (non-randomised) clinical trials, prospective and retrospective cohort studies, case-control or nested case control studies,

cross-sectional studies, case series and case reports were excluded.

Types of participants

Women in a subsequent pregnancy with a history of miscarriage. Miscarriage was defined as a spontaneous loss of pregnancy from the time of conception until 24 weeks of gestation.⁵⁴

Types of interventions

All types of non-pharmacological interventions such as psychological, emotional, information or support group interventions, either alone or in combination with another control intervention; for example, standard care or other type of intervention.

Outcomes

Trials reporting quantitative outcome data were included. The primary outcome was levels of perceived stress which was defined as 'the feelings or thoughts that an individual has about how much stress they are under at a given point in time or over a given time period'.⁵⁵ The secondary outcomes were: (1) levels of cortisol which was measured in saliva, urine, blood or hair; (2) levels of perceived anxiety which was defined as 'the stable tendency to attend to, experience and report negative emotions such as fears, worries and anxiety across many situations'⁵⁵ and (3) levels of perceived depression which was defined as a 'depressed or sad mood, diminished interest in activities which used to be pleasurable, weight gain or loss, psychomotor agitation or retardation, fatigue, inappropriate guilt, difficulties concentrating as well as recurrent thoughts of death'.⁵⁶ Secondary outcomes had to also be measured preintervention and postintervention.

Information sources and search

A total of 13 medical, psychological and social electronic bibliographic databases were searched: PubMed, Cochrane Library, CENTRAL, EMBASE, Web of Science (Web of Knowledge), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Maternity & Infant Care Database, Science Direct, Elton B. Stephens Co (EBSCOhost), ProQuest Nursing and Allied Health Source, CLINICAL TRIALS, Journal Storage (JSTOR) and Clinical trials websites. The reference lists of potential studies were also screened to identify other relevant studies. Keywords and Medical Subject Headings (MeSH) were used to identify studies related to miscarriage and stress (see online supplementary file 2). The date of the last search was 2 April 2016. There were no restrictions by study design, setting and country. All studies in English language were included. The literature search was limited by date (from January 1995 to April 2016).

Study selection

Search results were screened by two reviewers (ISLC, KM), first by titles and then by abstracts. Discrepancies were resolved with other reviewers (SM, KOD). Eligibility criteria of all potential studies were assessed using

the 'Data collection form for intervention reviews: RCTs only from April 2014' (by ISLC)⁵⁷ (see online supplementary file 3). Due to the variability in definitions of the condition, studies were included where the following terms appeared in their titles: *'miscarriage'*, *'pregnancy loss'*, *'perinatal loss'*, *'spontaneous abortions'*, *'early miscarriage'* and *'first trimester miscarriage'*. They were excluded when the following terms appeared: *'stillbirth'*, *'recurrent miscarriage'*, *'fetal death'*, *'infertility'*, *'subfertility'*, *'IFV'*, *'perinatal death'*, *'missed abortion'*, *'induced abortion'*, *'ectopic pregnancy'*, *'pregnancy wastage'*, *'oxidative stress'*, *'antioxidants'* and *'Intimate partner violence'*. Recurrent miscarriage was excluded because of the differences in the aetiology, diagnosis and therapy between other types of losses.^{58 59} No study was excluded for not identifying the outcome of interest in either title or abstract.⁶⁰

ENDNOTE X7 was the reference management software used to import, classify and analyse all citations in this systematic review. All citations from each database were automatically imported to ENDNOTE and then saved by electronic database and date of searching. Abstracts were also imported when they were available. Data collection was completed by one reviewer using data extraction forms and a second reviewer (SM) independently checked content. Definitions of the condition were obtained from abstracts or reading full reports of the studies. When miscarriage was analysed as a composite with other adverse pregnancy outcomes such as stillbirth or perinatal death, contact with the authors was made by email to try to obtain subsamples of the full datasets. Data extraction forms by the Cochrane Consumers and Communication Review Group⁶¹ were used to describe main characteristics, methodology and main results (see online supplementary file 4). A summary of the outcomes and the measurement of each outcome was assessed using the outcome matrix of the 'Outcome Reporting Bias of Trial' (ORBIT)⁶⁰ (see online supplementary file 5). Risk of bias was assessed using the 'Assessment of Risk of Bias' by the Cochrane Bias Methods Group⁵⁷ (see online supplementary file 6).

RESULTS

A total of 4140 citations were identified through database searches and 8 were identified through other sources. After duplicates were removed, 3325 citations were identified during the screening process (see figure 1).

A total of 17 RCTs and 2 clinical controlled trials (CCTs) were found in this review. This systematic review found no RCT which met all the inclusion criteria. Of the 17 RCTs, 10 were excluded for a variety of reasons including: no outcome of interest, medical intervention instead of non-medical interventions or pregnancy loss defined as a loss later than 24 weeks (table 1). Even though a number of studies (n=7) carried out non-pharmacological interventions to reduce levels of stress, anxiety or depression in women who have had miscarriage, those were excluded from the systematic review because women were

not pregnant at the time of the study or because miscarriage was analysed as a composite variable including other types of perinatal loss such as stillbirth or neonatal death (table 1). Furthermore, even though it was part of our initial objectives, this review did not find evidence of any RCTs that measured biomarkers of stress, such as cortisol, to assess the effect of psychological interventions in this population. As a consequence, no results were included in this systematic review.

Although none of the remaining RCTs met the full inclusion criteria (n=7) (see table 1), they have useful information for health professionals who are working in the area of pregnancy loss. In summary, only one RCT studied women while they were pregnant,⁶² but miscarriage was analysed as a composite variable with perinatal neonatal death. More than half of the RCTs identified were pilot or feasibility studies⁶²⁻⁶⁵ and had a small sample size with low statistical power. The most frequently measured outcomes were depression, anxiety, stress and grief (see online supplementary file 5). Levels of perceived stress were measured by four RCTs.⁶³⁻⁶⁶ Results of the RCTs varied, with some suggesting a positive reduction in levels of stress and depression when women took part in psychological interventions compared with a control group (see online supplementary file 4). Other studies found no change or did not reach statistically significant results on psychological outcomes (see online supplementary file 4). Supporting files describing main characteristics, outcome matrix and risk of bias of those relevant seven RCTs can be found online (see online supplementary files 4, 5 and 6). These supportive materials might help clinicians, researchers and decision-makers to increase the awareness of the available supportive interventions in the area of pregnancy loss as well as the lack of evidence or methodological quality in these types of studies.

DISCUSSION

The aim of this review was to systematically assess the effect of non-pharmacological interventions to reduce levels of stress in pregnant women who have had a miscarriage in their previous pregnancy. Unfortunately, no RCT met our inclusion criteria. The results of this review were unexpected given that first, several studies have previously reported the psychological impact on pregnant women with a history of miscarriage^{43 67 68} and second, because relevant institutions and organisations in the area of clinical health practice have reported the need of good-quality, adequately powered RCTs to evaluate interventions aimed at tackling moderate to severe psychological disorders in the pregnant population.^{6 69}

Comparison with other studies

There is an agreement in the literature that women who miscarry may suffer from psychological morbidities after pregnancy loss and in a subsequent pregnancy.⁷⁰⁻⁷² However, there are important limitations when summarising this evidence such as a lack of a comparison

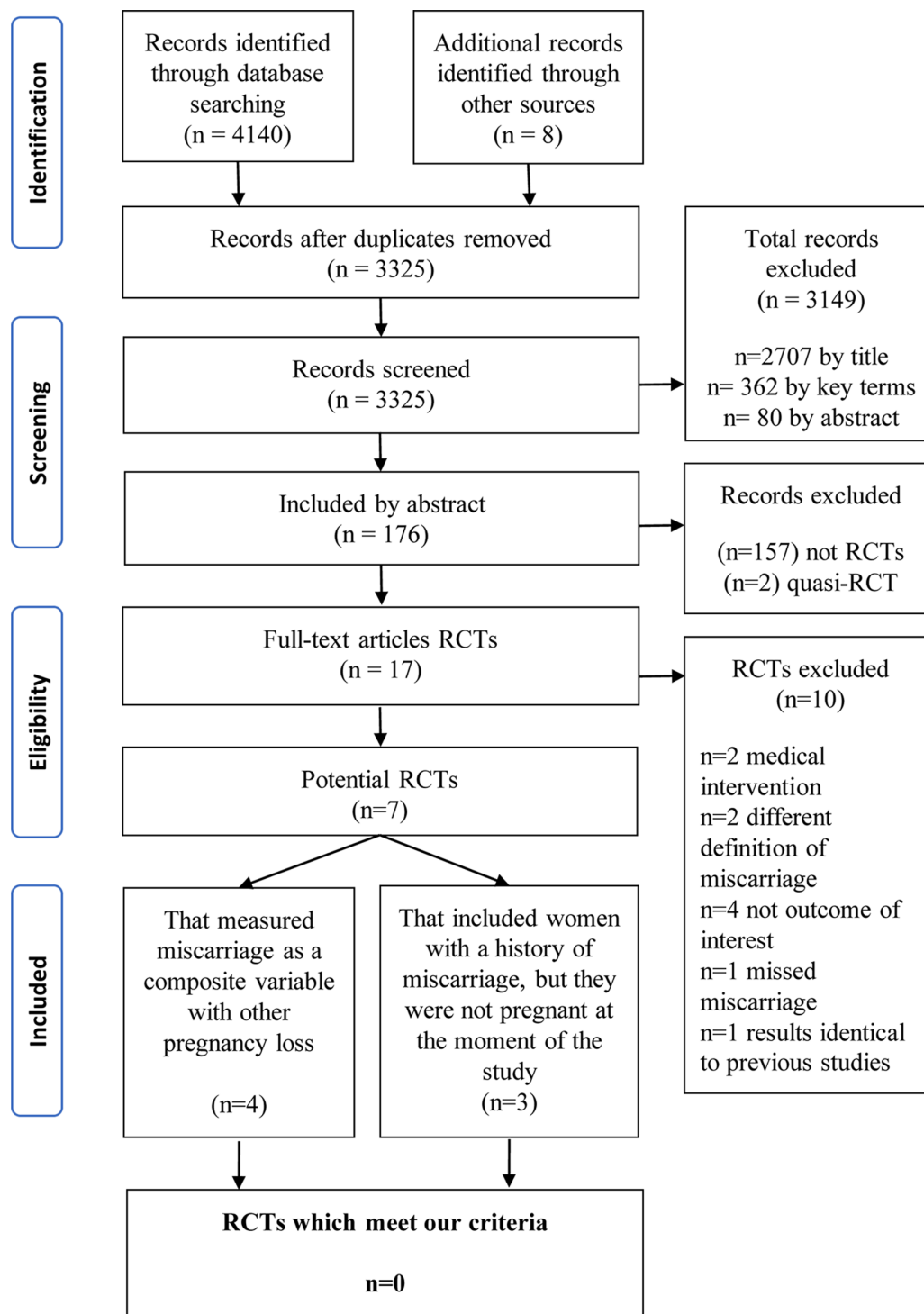


Figure 1 Flow diagram of the selection of the studies. RCTs, randomised controlled trials.

group within these studies or the overlapping of depression and anxiety symptoms and disorders.²² Furthermore, levels of stress were not assessed in women following miscarriage or in subsequent pregnancy in any of the reviews identified.^{25 71 72}

According to the most recent Cochrane systematic review, which assessed the effectiveness of non-pharmacological interventions on women with a history of miscarriage, only six randomised controlled studies assessed the

effect of psychological well-being interventions in women who experienced miscarriage.⁷³ None of them were carried out in women who were pregnant at the time of the study. These studies were also limited by a lack of power, unclear blinding or no blinding, heterogeneity between types of psychological follow-up and small sample size. Murphy *et al* (2012) concluded that not enough evidence was achieved to state if psychological interventions were beneficial for women who miscarry.⁷³

Limitations of the study

As with other type of studies, this review is not free of limitations. First, only one RCT included pregnant women despite previous pilot RCTs assessing non-pharmacological interventions to reduce levels of stress, anxiety and depression had included pregnant women as their target population.^{74–76} Historically, pregnant women have been excluded from clinical research due to potential ethical considerations such as (1) they are classified as a vulnerable group, (2) the possible risk of harming the fetus or (3) the complicated physiology during pregnancy.⁷⁷

Several efforts have been made to encourage researchers and clinicians to challenge these limitations and to include pregnant women in clinical research.⁷⁸ The basic principles in ethical foundation for including pregnant women in clinical research are: (1) the need for evidence-based knowledge of effective treatments during pregnancy; (2) the uncertain risk of not treating or undertreating a mother's condition and (3) the ethical justification of the possible benefits of participating in research.⁷⁸ As Macklin (2010) stated 'the next logical-and ethical-step is the enrolment and retention of pregnant women in clinical trials'.⁷⁹

Another limitation identified when undertaking this review was the different definitions of miscarriage found in the literature during the selection process. Definitions of miscarriage vary significantly between countries, professional bodies and clinical guidelines.⁸⁰ This variety of definitions made it difficult to compare and to evaluate the evidence between different countries in this field.⁸⁰

As important as the lack of an international concordance between definitions, this review found that some RCTs pooled together the results from miscarriage with other types of perinatal death such as stillbirth or neonatal death. One of the possible limitations is that, as per protocol, interventions carried out among women with recurrent miscarriage and/or perinatal death, or as a composite variables, were excluded in the screening process. It is reported that pregnancy loss and perinatal death have shown different psychological reactions to the loss.^{81–83} Moreover, the impact that a specific intervention might have on psychological well-being may differ as women are managed differently in a subsequent pregnancy depending on the type of pregnancy loss they have experienced.^{84 85} For instance, more resources are invested in women with recurrent miscarriage,⁸⁶

Table 1 List of all RCTs and CCTs (n=19) and reason for exclusion

Authors, year	Pregnant*		All RCTs and CCTs studies Reason for exclusion
	Yes	No	
CCTs (n=2)			
1. Klein <i>et al</i> , 2012 ⁹⁷		✓	Partially randomised patient design
2. Séjourné <i>et al</i> , 2011 ⁹⁸		✓	Quasi-RCT
RCTs (n=10)			
3. Adolfsson <i>et al</i> , 2006 ⁹⁹		✓	No outcome of interest included
4. Huffman, 2015 ¹⁰⁰		✓	No outcome of interest included
5. Lok, 2006 ⁷⁰		✓	Results are identical than Kong, 2014
6. Klinitzke <i>et al</i> , 2013 ¹⁰¹		✓	No outcome of interest included
7. Kong <i>et al</i> , 2013 ¹⁰²		✓	Medical intervention
8. Lee <i>et al</i> , 2001 ¹⁰³		✓	Medical intervention
9. Neugebauer <i>et al</i> , 2007 ¹⁰⁴		✓	Pregnancy loss later than 24 weeks
10. Neugebauer <i>et al</i> , 2006 ¹⁰⁵		✓	Pregnancy loss later than 24 weeks
11. Nikcević <i>et al</i> , 2007 ¹⁰⁶		✓	Missed miscarriage
12. Swanson, 1999 ²⁷		✓	No outcome of interest included
RCTs (n=7)			
13. Côté-Arsenault <i>et al</i> , 2014 ⁶² ✓			Pregnancy loss as a composite variable
14. Johnson <i>et al</i> , 2016 ⁶³		✓	Pregnancy loss as a composite variable
15. Kersting <i>et al</i> , 2013 ⁶⁶		✓	Pregnancy loss as a composite variable
16. Kersting <i>et al</i> , 2011 ⁶⁵		✓	Pregnancy loss as a composite variable
17. Kong <i>et al</i> , 2014 ¹⁰⁷		✓	Not pregnant at the time of the study
18. Lee <i>et al</i> , 1996 ⁶⁴		✓	Not pregnant at the time of the study
19. Swanson <i>et al</i> , 2009 ²⁸		✓	Not pregnant at the time of the study

*Subsequent pregnancy after miscarriage. Not including pregnancy which resulted in miscarriage.
CCTs, clinical controlled trials; RCTs, randomised controlled trials.

and supportive care is regularly offered to women with unexplained recurrent miscarriage.^{48 87–89} Consequently, reporting composite results might mislead the evidence in this research area.

Studies also illustrate that there are no differences between gestational age at pregnancy loss and adverse psychological outcomes.^{37 90 91} Hutti *et al* (2015) found no statistically significant differences between type of loss and grief, anxiety, depression or post-traumatic stress disorders among women in their subsequent healthy pregnancy.⁹² In addition, greater grief intensity was associated with increased pregnancy-specific anxiety, depression symptoms and PTSD. As a result, alternative approaches suggest to evaluate psychological outcomes in subsequent healthy pregnancies after a loss such as adopting the theoretical framework of perinatal grief intensity.^{93 94}

Implications and conclusion

It is commonly perceived that empty reviews, that is, systematic reviews that find no studies eligible for inclusion, do not provide additional information that can be used by clinicians and other decision-makers.⁹⁵ However, some authors argue that empty reviews can be of critical importance (1) to raise awareness of the gaps in the evidence in a particular area of interest for either clinicians, researchers and decision-makers, (2) to know who is interested in the area and (3) to indicate the state of research evidence at a particular point in time.^{95 96} In particular, this review is clinically important because it might help encourage the development and implementation of well-designed clinical trials for assessing non-pharmacological interventions on pregnant women who have had miscarriage.

In conclusion, it is accepted that miscarriage affects some women's psychological well-being, increasing their levels of stress after a single experience. It is also considered that previous miscarriage may be a factor in aggravating levels of stress in a subsequent pregnancy. There is a potential risk that women who have experienced miscarriage may be at risk for maternal stress during their subsequent pregnancy which in turn is associated with adverse pregnancy-related outcomes. To date, few studies have assessed the effect of non-medical interventions in women after pregnancy loss. Moreover, none of the RCTs, which were identified in this review, included pregnant women in their subsequent pregnancy after miscarriage. Therefore, there is a need for targeted, standardised, high-quality and powered RCTs that can provide reliable and conclusive results to determine effective psychological and support interventions for this vulnerable group.

Contributors KOD and SM conceived the study. KOD, SM and ISLC participated in its design. ISLC and KM independently screened and selected the studies. KOD and SM resolved discrepancies when they arose in the selection of the studies. ISLC completed the data extraction forms for the selected studies and SM independently checked the content. All authors helped draft the manuscript. All authors read and approved the final manuscript. KOD is the lead author.

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Data sharing statement The ENDNOTE library and the excel sheet to collect studies included in data repository websites used in the search strategy are available from the corresponding author on reasonable request.

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